Remarks

Claims 1 and 2 are pending. In view of the following remarks, further consideration and allowance of the claims are believed to be merited and are respectfully requested.

Telephone Interview

Applicants' undersigned attorney spoke with Examiner Bianco by telephone on April 27, 2006. The Examiner indicated that she had not reconsidered her 103 rejections of claims 1 and 2 in light of the amendment to specify "differentially removing high molecular weigh protein," because of her decision to reject those claims as lacking support for said amendment. However, Examiner Bianco indicated that should support be shown in the present amendment that she would reconsider the 103 rejections in view of the previous amendment.

Rejections under 35 U.S.C. § 112

Claims 1 and 2 are rejected as allegedly failing to comply with the written description requirement due to the recitation of "differentially removing," which the Office believes is not supported in the specification. The Office Action states that the specification as originally filed does not support differentially removing proteins from the blood, and that the as-filed application does not provide written description that reasonably conveys what applicant encompasses by the step of differentially removing.

Applicants respectfully traverse this rejection. Initially, it is important to note that in claim 1, the step of "differentially removing" refers to "high molecular weigh proteins." The as-filed application teaches "several plasma differential separation

techniques" on page 8, line 15 to page 11, line 16. More specifically, the specification teaches the use of "plasma differential filtration", which is described as passing the plasma through a filter eliminating proteins according to the pore size of the membranes (page 10, lines 20-26). It is recognized in the art that the pore size of a membrane is related to the molecular weight of the substance retained. The attached print-out of the STERLITECH Corporation web page entitled "General Filtration: Frequently Asked Questions" describes the art-recognized relationship between pore size and molecular weight (page 4 of 5 of Exhibit 1). Similarly, the attached print-out of the MILLIPORE web page relating to separation technologies describes the known relationship between filter pore size and molecular weight of the species retained or passed through (page 2 of 4 of Exhibit 2)). Thus, one of skill in the art would recognize that the application teaches the use of filters with pore sizes that differentially remove high molecular weigh proteins.

The application as filed teaches and exemplifies the use of filters that differentially remove high molecular weight proteins. All of examples 1, 2 and 3 (diabetic gangrene of the foot) applied "membrane differential separation" (also described as "differential filtration" on page 18, lines 10-14) to differentially remove high molecular weight proteins. For example, fibrinogen, immunoglobulins and low density lipoprotein cholesterol were reduced (removed) while total protein was only affected slightly (page 14, line 8 to page 15, line 19). There is no basis to believe that one of skill in the art would not recognize that these are descriptions of methods of differentially removing high molecular weight proteins. Because there is evidence that those of skill in the art would recognize the description of the claimed method in the application as filed,

and because there is no evidence that they would not, the application should be recognized by the Office as describing a method of differentially removed high molecular weigh protein. Thus, withdrawal of this rejection is believed to be merited and is respectfully requested.

Rejection under 35 U.S.C. § 103

Claim 1 is rejected as allegedly obvious over Georgadze et al.

With respect to the Georgadze et al. the examiner points out that this document describes plasmapheresis treatment which may be used for the treatment of ischemia in the lower extremities of diabetics. In the view of the examiner the reference discloses that the plasmapheresis corrects the biochemical and coagulation parameters of the blood and thereby preserves the extremity from amputation in most patients.

The examiner concludes that with respect to the treatment of the foot it would have been obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot since the foot is obviously a lower extremity. According to the Examiner, such treatment would be beneficial to preserve the foot from amputation. Regarding the specific removal of high molecular weight protein, the examiner asserts it would have been within ordinary skill to choose a method to remove proteins of any desired size, such as high molecular weight proteins, using the method of Georgadze et al.

Claim 1 recites that the claimed method of treatment differentially removes high molecular weight proteins from the blood. The recitation of this feature illustrates a non-obvious distinction over the cited Georgadze et al. reference.

Georgadze et al. does not suggest the selective removal of high molecular weight proteins in that it fails to mention this approach and it fails to provide any motivation for selective removal. Furthermore, it can be concluded from the first page 2nd paragraph that the centrifugation plasmapheresis technique described in the Georgadze et al. document leads to the non-selective elimination of numerous types of blood components that can contribute to diabetic ischemia. This procedure is, by its very nature, non-selective. Thus, not only is there no explicit suggestion, there is no implicit suggestion in Georgadze et al. to selectively remove large molecular weight proteins. In contrast, the treatment according to the invention selectively removes high molecular weight proteins and preferably low density lipoprotein, cholesterol, alpha-2-macroglobulin and similar high molecular weight proteins.

Furthermore Georgadze et al. teaches that a medicament Rheopolyglukin was used as an infusion substance (see page 2, 2nd paragraph of English translation). Such a medicament is not used in the treatment according to the present invention. While this component of the Georgadze et al. method is not stated in the reference to be required for success, it is unpredictable that the method would work without this component. Thus, because the reference used Rheopolyglukin, and suggests its future use (see page 5, item 2 of the Conclusions), the reference does not suggest a method in which it is not used. Since the method of the invention does not use this component, the invention is not suggested by the reference. The current Office Action does not explicitly address this argument previously made by applicants. Since it is relevant to the issue of obviousness, applicants respectfully request that the Examiner address it explicitly.

The present invention uses method steps that differ from and are not suggested by Georgadze et al., namely, that high molecular weight proteins are preferentially removed from the blood of the patient. After that, the blood is reinfused into the patient and thereby the diabetic ischemia of the foot is treated. Georgadze et al. has the disadvantage of being less selective than the present invention. As explained above the treatment according to the invention is very selective compared to the gravitational plasmapheresis treatment according to the Georgadze et al. reference.

The conclusion of the in the office action that it was obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot is wrong for the present claim because Georgadze et al. discloses a totally different plasmapheresis procedure compared to the claimed invention. The procedure disclosed in the cited art is a technique in which toxic substances are removed from the blood, but not by the selective removal of large molecular weight protein components of the blood. Since there is no suggestion in Georgadze et al. of any advantage to the differential removal of high molecular weight protein, there is no motivation in this reference to do so. In the absence of such motivation, the art cannot render obvious claim 1.

Claims 1 and 3 are rejected as allegedly obvious over Georgadze et al. in view of Malchesky et al.

There is no motivation in Malchesky et al. to apply its teaching to the method of Georgadze et al. or in the context of diabetic ischemia of a foot. There is also no motivation in Georgadze et al. to apply the teaching of Malchesky et al. to its method or

in its context of use. Neither reference is directed to the science or practice of hemorheology. Georgadze et al. is focused on purification of the blood, not on the improvement of the general state of blood fluidity (hemorheology), which is what the present invention is concerned with. Likewise, Malchesky et al. is directed to the treatment of diseases associated with specific blood solutes, not the general state of blood fluidity. In fact, Malchesky specifically mentions diabetic hypertriglyceridemia, because it is associated with elevated triglycerides (a specific blood solute), but does not mention diabetic ischemia because it would not have been apparent that the methods disclosed would treat diabetic ischemia. Thus, there is no suggestion in Malchesky et al. that the method taught therein would have any relevance to diabetic ischemia. Since there is no suggestion in Georgadze et al. of the relevance of hemorheology in the treatment of diabetic ischemia or of differential removal of large proteins, and since there is no suggestion in Malchesky of either 1) any value to changing blood fluidity or 2) applicability to diabetic ischemia of a foot, there is no motivation to use the technique of Malchesky et al. to modify the method of Georgadze et al. to treat diabetic ischemia.

Furthermore, please see the previously submitted letter of Dr. Schmid-Schönbein. Dr. Schmid-Schönbein is the former Director of the Department of Physiology, University of Aachen, and an internationally recognized expert in rheology. Also previously submitted was a list of 198 references identified on PubMed of which Dr. Schmid-Schönbein is an author. The previous letter explains the concept of hemorheology and notes the failure of the prior art to suggest its application for the treatment of diseases such as diabetic ischemia of a foot. The letter of Dr. Schmid-

Schönbein also acknowledges the significant contribution of the present invention to the art of treating diabetes.

Furthermore, the fact that others have adopted the method of the claims, means that the present invention satisfies a previously unsatisfied need. This is shown in the previously submitted papers of Richter et al., Extracorporeal fibrinogen adsorption--efficacy, selectivity and safety in healthy subjects and patients with foot ulcers, Transfus Apher Sd. 2002 Feb;26(1): 15-27; and Klingel et al., Rheopheresis in patients with ischemic diabetic foot syndrome: results of an open label prospective pilot trial, Ther Apher Dial. 2003 Aug;7(4):444-55.

Since neither reference cited in the combination discloses or suggests any value for changing blood fluidity (hemorheology), neither suggests the aspect of the claimed invention that is missing from the other reference. Because the references taken alone or together do not suggest the application of size-based differential removal of high molecular weight proteins from the blood to treat diabetic ischemia of a foot, the invention of claims 1 and 2 is not obvious over the art.

No new matter is believed to be added by any of the preceding amendments. Thus, consideration and allowance of the pending application are respectfully requested. The Examiner is invited to contact the undersigned counsel by telephone if such contact would expedite prosecution.

No additional fee is believed due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Gwendolyn D. Spratt
Registration No. 36,016

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

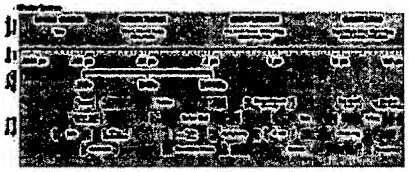
Gwendolyn D. Spratt — Date: 7-6-06

MILLIPORE

SEARCH

HOME | ABOUT MILLIPORE | BIOSCIENCE | BIOPROCESS | APPLIED MARKETS | CONTACT US | ONLINE STORE

PRODUCT CATALOGUE



- Specifications

Millipore Separation and Purification Technologies

Millipore technology provides products, systems and application techniques for the analysis and purification of fluids by filtration through microporous and ultrafiltration, reverse osmosis and nanofiltration membranes .

Millipore microporous membrane and depth filtration has long been an integral and critical step in industrial processing. In pharmaceutical manufacturing, membrane and depth filters remove particles, viruses, colloids, bacteria, and other types of cellular organisms from solutions throughout the process, from the purification of central system water to final product sterilization. Microporous membranes may be operated on normal flow (dead-ended) or tangential flow (cross-flow) filters for a broad range of solid/liquid or solid/gas separations. Millipore membrane filtration is also widely used as an analytical tool for the collection, identification and measurement of particles and microorganisms.

Millipore ultrafiltration membranes are operated in tangential flow filters and are used for molecular and viral separations. They are used to concentrate and purify a wide variety of biological and chemical process fluids, to concentrate and purify or remove viruses and other colloid suspensions, and to remove very fine particulate contamination for fluid clarification.

Millipore reverse osmosis (RO) and nanofiltration (NF) membranes are used to separate water and other very small molecules from ionic species and larger molecules. RO and NF membranes are operated in tangential flow filters and are used to concentrate aqueous solutions of small solutes and salts. NF membranes are also used to remove monovalent salts from aqueous solutions of small solutes and for the removal of viruses from proteins containing solutions.

Microfiltration
Microfiltration is the process of removing contaminants in the 0.025 to 10.0 µm range from fluids by passage

CUSTOMER SUPPORT

- Order Service
- Technical Service
- Local Millipore Office
- Local Application Specialists
- Retrieve Forgotten Password
- RSS Feeds XML | FOD

LOGIN

Username

Password

Login | Register

ONLINE STORE

- Catalogue
- How to Order
- eCommerce FAQs
- Availability and Pricing
- Register
- Quick Purchase
- Where's My Order?
- Procurement System Integration
- Manage Account Settings

through a microporous medium such as a membrane filter. Although micron-sized particles can be removed by use of non-membrane or depth materials such as those found in fibrous media, only a membrane filter, having a precisely defined pore size, can ensure quantitative retention.

The retention boundary defined by a membrane filter can also be used as an analytical tool to validate the integrity and efficiency of a system. For example, in addition to clarifying or sterilizing filtration, fluids containing bacteria can be filtered to trap microorganisms on the membrane surface for subsequent culture and analysis.

Membrane filters can be used for final filtration or prefiltration, whereas a depth filter is generally used in clarifying applications where quantitative retention is not required, or as a prefilter to prolong the life of a downstream membrane.

Membrane and depth filters offer certain advantages and limitations, and can complement each other when used together in a microfiltration process system.

In all filtration applications, the permeability of a filter medium can be affected by the chemical, molecular or electrostatic properties of the filtrate.

Ultrafiltration

Ultrafiltration is the process of separating extremely small particles and dissolved molecules from fluids. The primary basis for separation is molecular size although secondary factors such as molecule shape and charge can play a role. Materials ranging in size from 1,000 to 1,000,000 molecular weight are retained by ultrafilter membranes, while salts and water will pass through. Colloidal and particulate matter can also be retained.

Ultrafiltration membranes are used to purify and collect both material passing through the filter and material retained by the filter. Materials smaller than the pore size rating pass through the filter and can be depyrogenated, clarified and separated from high molecular weight contaminants. Materials larger than the pore size rating are retained by the filter and can be concentrated or separated from low molecular weight contaminants.

Ultrafiltration membranes are usually operated in a tangential flow mode—feed material sweeps tangentially across the upstream surface of the membrane as filtration occurs— thereby maximizing flux rates and filter life. These systems offer the advantage of long life because ultrafilter membranes can be repeatedly regenerated with strong cleaning agents.

Microporous membranes can also be operated in a tangential flow mode. This provides the ability to purify and concentrate particulate materials, such as bacteria, yeast, and animal cells where large molecules must pass through the filter.

Chromatography

Millipore now also offers liquid chromatography for pharmaceutical and biotech applications, for the purification of proteins, enzymes, peptides and other biologics and synthesized organic molecules.

Millipore has an extensive product range, through media, columns and systems for LPLC and HPLC, from laboratory to process scale, offering a single source for all the key elements of chromatographic processes.

Reverse Osmosis and Nanofiltration

Reverse osmosis and nanofiltration are the processes of separating very low molecular weight molecules (typically <1500 Daltons) from solvents (most often, water). The primary basis for separation is rejection of solutes by the membrane on the basis of size and charge. Unlike UF membranes, RO and NF membranes retain most salts as well as uncharged solutes. NF membranes are a class of RO membranes which pass monovalent salts but retain polyvalent salts and uncharged solutes larger than ~400 Daltons.

RO and NF membranes are operated in tangential flow mode to concentrate small solutes by removing water. NF membranes can be used in diafiltration mode to remove monovalent salts from larger solutes in aqueous solutions and for the removal of viruses from proteins containing solutions.

Depth, Surface, and Membrane Filters

For most high volume filtration applications, the properties of membrane and depth filters are clearly complementary. Depth filtration allows the removal of a bulk of particles economically. Surface filtration combines relatively high dirt-holding capacity with clearly defined retention characteristics. Membrane filtration permits complete removal of particles and micro organisms above a certain size as qualified by preestablished specifications and testing regimen. By using a depth filter for upstream processing and a membrane filter for final filtration, it is possible to get an optimum combination of retention efficiency, high dirt capacity and processing economies.

Depth Filter

Structure

Depth filters have a fibrous, granular or sintered matrix that produces a random porous structure. Particles become trapped in the tortuous network of flow channels. The principle retention mechanisms are random adsorption and mechanical entrapment throughout the depth of the matrix.

Construction

Filtration media may be wound cotton, polypropylene, rayon cellulose, fiberglass, sintered metal, porcelain or diatomaceous earth.

Performance

Depth filters characteristically exhibit high dirt-holding capacity and will also retain a large percentage of contaminants smaller than their pore size rating. They are generally less expensive than membrane filters.

Surface Filter

Structure

Surface filters have a multilayer filter medium constructed of glass or polymeric microfibers. Particles larger than the spaces within the filter matrix are retained, primarily on the surface. Smaller particles tend to be trapped within the matrix, giving the surface filter properties of both a membrane and a depth filter.

Construction
Typically, surface filters are constructed of polypropylene, cellulose/resin bonded paper , or fiberglass/paper.

Performance
Due to their multiple layers of pleated media, surface filters exhibit a high dirt-holding capacity. As a result of their "controlled" pore structure, they provide more predictable retention than depth filters. They are generally less expensive than membrane filters.

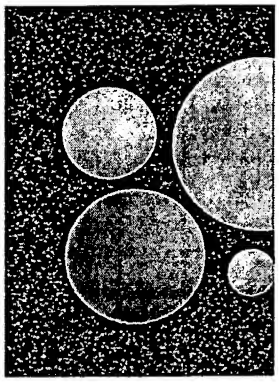
Membrane Screen Filters

Structure
Membrane filters may be thought of as a geometrically regular porous matrix. Particles are retained on the surface or within a given fraction of the membrane's thickness, primarily by a size exclusion (sieving) mechanism. All particles and microorganisms larger than the pore size will be retained.

Construction
For critical submicronic and macromolecular separations, these filters are constructed of cast polymeric membranes.

Performance
Predetermined, controllable pore size limits the largest particle than can pass through a membrane filter. Retention efficiency is independent of flow rate and pressure differential. Membrane filters exhibit low hold-up volume and are non-fiber releasing.

STERLITECH Corporation



Sterlitech™ Membran

General Filtration: Frequently Asked Questions

Click here to view the Filtration Spectrum.

Q. What is a membrane filter?

A membrane filter is a matrix with channels which act as a screen and retain particles larger than the filter on the surface of the membrane. Membrane filters allow the retention of sub-micron particles and organisms.

Filtration definations and relative pore size	
MF	0.1 - 5.0 micron
UF	0.01-0.1 micron
NF, RO	0.001 (theoretical)

Note that pores have not been observed in RO or NF membranes using a microscope.

Click here for an excellent chart showing pore size relative to retained particles (Courtesy of GE Osmonics).

top of page

Q. What is the maximum temperature for the different filter membranes?

The maximum operating temperatures for Sterlitech filter membranes are listed below.

- Sterlitech Silver Metal - 427°C
- Sterlitech Ceramic - 350°C
- Sterlitech Polycarbonate Track Etch - 140°C
- Sterlitech Polyester - 140°C
- Sterlitech Nitrocellulose (MCE) - 130°C
- Sterlitech Nylon - 180°C
- Sterlietch Polyethersulfone (PES) - 180°C
- Sterlitech Polypropylene - 82°C
- Sterlitech Cellulose Acetate - 135°C
- Sterlitech PTFE (Laminated) - 130°C
- Sterlitech PTFE (Unlaminated) - 260°C
- Sterlitech PVC Data not available

top of page

Q. What is hydrophilic vs hydrophobic membrane?
Hydrophilic filters posses an affinity for water and can be wetted with almost any liquid. Sterlitech carries a wide variety of hydrophilic membranes, including:

- Silver Metal
- Polyethersulfone (PES)
- Glass Fiber
- Polycarbonate Track Etch (PCTE)
- Polyester (PETE)
- Mixed Cellulose Esters (MCE)
- Nylon
- Cellulose Acetate
- PVC Silica-Free

Hydrophobic filters lack an affinity for water and are best suited for venting applications. Example of hydrophobic filters are Sterlitech polypropylene membranes and Sterlitech PTFE (Teflon®), either laminated or unlaminated.

top of page

Q. How is the performance of a filter measured?

Design and material selection determines the performance of a filter. Three important measures of filter performance are flow rate, throughput and bubblepoint, defined as follows:

Flow Rate: Determines the volume of liquid or air that will flow through the filter at a fixed pressure and temperature. This is usually displayed as ml/minute/cm^2.

Throughput: Describes the dirt handling capacity of a filter. Namely, how long the liquid will continue to flow through the

membrane before the membrane clogs. The lower the flow rate and throughput, the longer it takes the researcher to complete the analysis.

Bubble point: A test to determine the integrity and pore size of a filter. The differential pressure at which a steady stream of gas bubbles is emitted from a wetted filter under specific test conditions. The bubble point test measures the largest pore. Bubble point is generally determined using water or an alcohol (methanol or isopropynol) and is displayed as PSI

top of page

Q. What variables affect the performance of a filter?

Viscosity: The viscosity of a liquid determines its resistance to flow; the higher the viscosity, the lower the flow rate and the higher the differential pressure required to achieve a given flow rate.

Porosity: The flow rate of a membrane is directly proportional to the porosity of a membrane, eg. the more pores, the higher the flow rate.

Filter Area: The larger the filter area, the faster the flow rate at a given pressure differential and the larger the expected filter throughput volume prior to "clogging for a given solution."

top of page

Q. How is pore size determined?

The pore size of a filter, normally stated in micrometers (µm), is determined by the diameter of a particle that is retained by the filter. This is determined using a challenge organism and/or bubble point testing.

top of page

Q. How are pore sizes rated?

A pore size rating is determined by the diameter of the particle that it can be expected to retain with a defined, high degree of efficiency. The rating is stated in **nominal** or **absolute** terms.

top of page

Q. What is the difference between nominal and absolute pore size ratings?

Nominal pore size rating describes the ability of the filter to retain the majority of the particles at the rated pore size and larger (60-9%). Glass fiber filters and screen filters are a good example of nominally rated filtration.

Absolute size rating describes the pore size at which a challenge organism of a particular size will be retained with 99.9% efficiency under strictly defined test conditions. Most membrane filters are rated as absolute terms.

top of page

Q. What organisms are used to determine pore size?

Pore Size	Challenge Organism
0.1 µm	Acholeplasma laidlawii
0.2 µm	Brevundimonas diminuta
0.45 µm	Serratia marcescens
0.8 µm	Lactobacillus species
1 µm	Candida albicans

top of page

Q. What is a bubble point test?

A test to determine the integrity and pore size of a filter. The differential pressure at which a steady stream of gas bubbles is emitted from a wetted filter under specific test conditions. The bubble point test measures the largest pore.

top of page

Q. What is a KD (kiloDalton)?

KD, or kD is the abbreviation for kiloDalton and is equal to 1,000 Molecular Weight Cut-Off (MWCO). A solution having a molecular weight of 1,000,000 would be equivalent to 1,000 KD. The table listed below gives a general relationship between kiloDalton to Microns (micrometers), Nanometers, and Angstroms:

KD's	Microns	Nanometers	Angstroms
1,000 KD	0.1 micron	100	1000
500 KD	0.02 micron	20	200
200 KD	0.01 micron	10	100
50 KD	0.004 micron	4	40
10 KD	0.0025 micron	2.5	25
5 KD	0.0015 micron	1.5	15

As a general rule, choose a membrane with a pore size (MWCO) that is less than half of the compound of interest.

top of page

Membrane Filter Main Page.

Sterlitech Corporation
22027 70th Ave. S

Kent, WA
98032-1911 USA
Tel: 877-544-4420
253-437-0844
Fax: 253-437-0845
info@Sterlitech.com

To order, call today: 1-877-544-4420
Or email: sales@Sterlitech.com

Free eNewsletter!